UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/989,896 | 12/12/97 | GEHRMANN M | 05552.1337-0 |

HM12/0807
FINNEGAN HENDERSON FARABOW
GARRET & DUNNER
1300 I STREET N W
WASHINGTON DC 20005-3315

| EXAMINER | |
|---|---|
| SAUNDERS, D | |
| ART UNIT | PAPER NUMBER |
| 1644 | 19 |

DATE MAILED: 08/07/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 5/11/00.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) 1-22, 25-33 is/are pending in the application.

Of the above, claim(s) 14-22 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-13, 25-33 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

**– SEE OFFICE ACTION ON THE FOLLOWING PAGES –**



★ U.S. GPO: 1996-410-238/40050

The amendment filed on 5/11/00 has entered no new matter. Following entry of this amendment claims 1-22 and 25-33 are pending. Claims 1-13 and 25-33 are under examination.

The drawing changes proposed on 5/11/00 (Paper 8) have been approved by the examiner.

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 is drawn to a protein, comprising an antigen binding region and an enzyme, while claim 2 in drawn to a carbohydrate. Claim 2 thus fails to further define the protein of claim 1.

Claims 2-3,5,12-13,30 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2, as amended is confusing as to what "comprises covalently bonded carbohydrates" because it is not clear what these are bonded to. To overcome this rejection as well as the above objection under 37 CFR 1.75© it is suggested applicant insert--further--before "comprises".

With respect to claims 2 and 30 the examiner previously rejected these as being inconsistent with base claim 1 )Paper 6, page 4). This rejection is maintained since an sFv fragment is monovalent, not multivalent. If applicant intends to embody a bivalent sFv enzyme

as disclosed at page 5, lines 31-33, then applicant should recite that there are dimers of the fusion protein. Since claims 3 and 30 are indefinite, dependent claims 5,12-13 and 32 are rejected.

Applicant's amendments and urgings of Paper 9 have overcome all other previously stated bases of rejection under 112, and paragraph.

The previously stated rejections under 35 USC 101 and 112, first paragraph have been overcome, due to applicant's claim cancellations and/or urgings.

Applicant's response with respect to the 112 second paragraph rejection of claim 30 has necessitated the following rejection of this claim under 35 USC 112, first paragraph.

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 30, which is not an original claim contains new matter not supported by the originally filed disclosure

Applicant's response of Paper 9 has indicated that claim 30 is intended to embody the dimeric form of an sFv-enzyme fusion protein, as disclosed at specification page 5, lines 31-33. Since "at lease one" as recited in claim 30, would include more than dimers, claim 30 is overly broad with respect to what is properly supported by the disclosure.

Claims 1-9,25-27,30 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al (Brit. J. Cancer 65,235,1992 or Seemann et al (EP0,501,215, English equivalent is CA2,062,047) in view of Huston et al and as necessary Bosslet et al

(EP0,040,097, English equivalent is US 5,591,828) and Eaton et al (EP0,392,745), for reasons of record in Paper 6.

Claims 11-12 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al or Seemann et al in view of Huston et al and as necessary Bosslet et al and Eaton et al as applied to claims 1-9,23-27,30 and 33 above, and further in view of Ong et al (Cancer Res.51,619,1991), Bagshawe et al (WO89/10140), an Huston et al (Methods Enzymol., 204,46,1991)., for reasons of reasons of record in Paper 6.

Claims 10,13 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al or Seemann et al in view of Huston et al and as necessary Bosslet et al and Eaton et al and further in view of Ong et al, Bagshawe et al and Huston et al as applied to claim 11-12 and 31-32 above, and further in view of Goochee et al (Biotechnol, 9,1347,1991), for reasons of record in Paper 6..

Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al or Seemann et al in view of Huston et al and as necessary Bosslet et al and Eaton et al as applied to claim 1-9, 23-27,30 and 33 above, and further in view of Bagshawe et al (WO 88/07378), for reasons of record in Paper 6.

Applicant's urgings in Paper 9 have been considered but are unconvincing.

Applicant's arguments in Paper 9, pages 21-22 have indicated that the sFv of Huston et al is not art recognized a functional equivalent of Fab, and that one could not have predicted that an

sFv would refold, particularly when linked to an enzyme domain, and that one world not have predicted that an sFv would have increased stability and might have a lower affinity than the Fab.

These urgings are unconvincing since sFv and Fab constructs are well recognized in the immunochenisty art as with having the function of binding to an antigen; the example reported by Huston et al (5,132,405) at col. 19 shows that the sFv has the same binding specificity as the parent antibody. Huston et al ( Methods... at page 48) teach that sFv is an analog of IgG of the Fab fragment thereof.

The arguments with respect to lack of predictability the proper refolding of an sFv molecule and with respect to lowered affinity of sFv molecule (by reference to page 55 of Huston et al's methods reference) merely focus an some isolated reported cases of lowered binding affinities of sFv analogue and their fusion proteins and ignore the over all teaching that sFv analogues can be constructed with binding properties equivalent to those of the parent antibody (Huston et al, methods at page 87). Huston et al further indicate refolding is not an issue ( methods at page 68, lines 5-8).

The argument that one would have expected that linkage to an enzyme domain would have resulted in a non-functional sFv domain is in convincing in light of Houston et al's teachings (methods page 87) that the fusion of effector domains to either chain terminus of the sFv appear to be practical without perturbation of the antigen combining site. Huston et al further indurate (methods page 83) that both the antigen binding activity and the effector activity in a fusion protein are retained; furthermore the binding affinity of the sFv segment of the

fusion protein is equivalent to the that of the parent IgG (Huston et al, methods at page 82). Applicant has offered no reason why a fusion protein containing an sFv and a pro-drug protein containing an sFv and a pro-drug activating enzyme would have been expected to have more problems.

It is further to be noted that the claims issued to Huston et al ('405) are directed to fusion constructs of an sFv and a third amino acid sequence (any effector) wherein the conformation permits one to have the biological (effector activity) of the third sequence as well as the antigen binding activity of the sFv. That such claim were given in the 405 patent is an indication that the office considered one would have a reasonable expectation of success without undue experimentation, in constructing fusion proteins with both antigen binding and effector activities. Since there would have been a reasonable expectation of success when making the modification according to the cited combination of prior art obviousness is maintained.

With regard to stability of the sFv-effector fusion proteins applicant has offered no reason as to why these would have been expected to be less stable than Fab-effector fusion proteins of the prior art. Application has offered no evidence that contradicts the teachings of Huston et al (405 at col. 4) that sFv proteins have increased stability. In any event stability is just one of several factors, including consideration of tissue penetratability that would have motivated one to make and use the instant fusion proteins.

Applicant's arguments pertaining to Eaton et al (pages 23-24) address this reference in isolation since the rejection has been made in the basis that this reference teaches a particular

pro-drug activating enzyme (beta-lactamase) and a source thereof which would have been recognized as following with in the genus of pro-drug activating enzymes. It is not necessary that Eaton et al teach other aspects of the claimed invention, since these are taught by other references of the combination.

With respect to providing galactosyl and/or mannosyl moieties on the constructs, applicant has argued that glycosylation would have been expected to result in a serious impact in stability, clearance rate, or affinity but has presented no basis for this assertion. To the contrary, Bagshawe et al and Ong et al teach that provision of such moieties improves clearance.

Other argument of applicant pertaining to the references merely address these in isolation by arguing what aspects(s) they each do not teach of applicant's invention, without accounting for the fact that the combination of references provide for all aspects of the invention.

The 101 and obvioisness type double patenting rejections of record have been withdrawn due to abandonment of the copending application.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant should cancel non-elected claims 14-22 in any after final response.

Any inquiry concerning this communication should be directed to D. Saunders at telephone number (703) 308-0196.

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644

Saunders/sg

8-1-00